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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,285	11/17/2003	James Thompson	MBHB00-873-1 (500.011)	5200

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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/715,285	THOMPSON ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 19, 2007 has been entered.

Claim 16 has been amended.

Claims 16-24 are pending in the instant application.

Claims 16-24 have been examined on the merits.

Response to Arguments

Applicants Amendment and Response filed April 19, 2007 have been considered. Rejections and/or objections not reiterated from the previous Office Action mailed October 19, 2006 are hereby withdrawn. Any arguments addressing said rejections and/or objections are moot. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Priority

It is noted that in the first sentence of the specification it is referenced that the instant application is a continuation of 09/866,316, which is a continuation-in-part of

09/103,636, which claims priority from Provision Application No. 60/082,404. First, the reference should be updated to reflect applications for patents that have issued or that have been abandoned. Second, due to the voluminous nature and number of the applications to which priority is claimed, Applicant are requested to point out with particularity where support for the instantly claimed invention may be found in one or more of the prior filed applications to which benefit is claimed, since such support is not readily apparent in the priority documents.

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

It is further noted the instant claims have been amended and are currently drawn to a chemically modified double stranded short interfering ribonucleic acid (siRNA) molecule comprising a sense strand and an antisense strand, wherein each strand is about 14 to about 24 nucleotides in length, wherein the antisense strand comprises about 14 to about 24 nucleotides that are complementary to a nucleotide sequence of a target RNA or a portion thereof; the sense and the antisense strand are 100% complementary to each other; either the sense or antisense strand comprise a 5'-cap, a 3'-cap or both a 5' and 3'-cap; and about 50 to 100 percent of the nucleotides of the

sense strand, the antisense strand, or both comprise a chemical modification wherein the chemical modification is 2'-fluoro, 2'-O-methyl, 2'H, or a combination thereof.

The instant application claims priority to a number of parent applications including USSN: 09/866,316, USSN 09/103,636, and Provision Application No. 60/082,404. Now then, referring to the parent applications, it does not appear that any of the priority application supports the invention as instantly claimed.

In summary, Applicants claim priority to a number of parent applications, however, none of the priority applications appears to have support for a chemically modified double stranded short interfering ribonucleic acid (siRNA) molecule comprising a sense strand and an antisense strand, wherein each strand is about 14 to about 24 nucleotides in length, wherein the antisense strand comprises about 14 to about 24 nucleotides that are complementary to a nucleotide sequence of a target RNA or a portion thereof; the sense and the antisense strand are 100% complementary to each other; either the sense or antisense strand comprise a 5'-cap, a 3'-cap or both a 5' and 3'-cap; and about 50 to 100 percent of the nucleotides of the sense strand, the antisense strand, or both comprise a chemical modification wherein the chemical modification is 2'-fluoro, 2'-O-methyl, 2'H, or a combination thereof. In fact, the term, "siRNA" does not appear to be recited in any of the parent applications. In this regard, the instant claims have been afforded priority to the filing date of the instant application, which is November 17, 2003.

If Applicants believe that they are entitled to an earlier priority date, the Examiner urges Applicant to specifically point where support can be found for the term "short

interfering ribonucleic acid (siRNA)" in any other applications Applicants claim priority to.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 recites the limitation "said nucleic acid" in line 2. There is insufficient antecedent basis for this limitation in the claim because claim 16, from which claim 21 depends recites, "ribonucleic acid". Replacement with the limitation, "said ribonucleic acid" would obviate the instant rejection.

Claim 24 recites the limitation, "A composition comprising the double stranded nucleic acid molecule of claim 16". There is insufficient antecedent basis for this limitation in the claim because claim 16, from which claim 24 depends recites, "double stranded short interfering ribonucleic acid". Replacement with the limitation, A composition comprising the double stranded ribonucleic acid molecule of claim 16" would obviate the instant rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The instant claims are drawn to a chemically modified double stranded short interfering ribonucleic acid (siRNA) molecule comprising a sense strand and an antisense strand, wherein each strand is about 14 to about 24 nucleotides in length, wherein the antisense strand comprises about 14 to about 24 nucleotides that are complementary to a nucleotide sequence of a target RNA or a portion thereof; the sense and the antisense strand are 100% complementary to each other; either the sense or antisense strand comprise a 5'-cap, a 3'-cap or both a 5' and 3'-cap; and about 50 to 100 percent of the nucleotides of the sense strand, the antisense strand, or both comprise a chemical modification wherein the chemical modification is 2'-fluoro, 2'-O-methyl, 2'H, or a combination thereof. In Applicant's Amendment filed April 29, 2007, Applicant's contend that support for the amendments can be found in the specification at various lines at pages 6, 7, 11, 17, and 18, for example. Now then, referring to the instant specification at pages 6, 7, 11, 17, and 18, it does not appear that the term, "short interfering ribonucleic acid (siRNA)" is supported.

In summary, the instant specification does not appear to support a chemically modified double stranded short interfering ribonucleic acid (siRNA) molecule comprising a sense strand and an antisense strand, wherein each strand is about 14 to about 24

nucleotides in length, wherein the antisense strand comprises about 14 to about 24 nucleotides that are complementary to a nucleotide sequence of a target RNA or a portion thereof; the sense and the antisense strand are 100% complementary to each other; either the sense or antisense strand comprise a 5'-cap, a 3'-cap or both a 5' and 3'-cap; and about 50 to 100 percent of the nucleotides of the sense strand, the antisense strand, or both comprise a chemical modification wherein the chemical modification is 2'-fluoro, 2'-O-methyl, 2'H, or a combination thereof. Specifically, the term, "short interfering ribonucleic acid (siRNA)" does not appear to be supported. In this regard, claims drawn to a chemically modified double stranded short interfering ribonucleic acid (siRNA) molecule appear to be new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 16-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al. (U.S. Patent No. 6,506,559), Zamore et al. (Cell, 2000 Vol. 101, pages 25-33), both made of record in the Office Action mailed October 19, 2006), or Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pp. 6877-6888, 2001), the combination in view of McCall et al. (U.S. Patent No. 6,277,634) and Matulic-Adamic et al. (U.S. Patent No. 5,988,203), both made of record in the Office Action mailed April 14, 2006.

Claim 16 is drawn to a chemically modified double stranded short interfering ribonucleic acid (siRNA) molecule comprising a sense strand and an antisense strand, wherein each strand is about 14 to about 24 nucleotides in length, wherein the antisense strand comprises about 14 to about 24 nucleotides that are complementary to a nucleotide sequence of a target RNA or a portion thereof; the sense and the antisense strand are 100% complementary to each other; either the sense or antisense strand comprise a 5'-cap, a 3'-cap or both a 5' and 3'-cap; and about 50 to 100 percent of the nucleotides of the sense strand, the antisense strand, or both comprise a chemical modification wherein the chemical modification is 2'-fluoro, 2'-O-methyl, 2'H, or a combination thereof. Claims 17-23 are dependent on claim 16 and include all the limitations of claim 16 with the further limitations wherein said cap comprises an inverted nucleotide; wherein said inverted nucleotide comprise an inverted deoxynucleotide; wherein said cap comprises an inverted abasic moiety; wherein said inverted abasic moiety comprises an inverted deoxyabasic moiety; and wherein said nucleic acid comprises one or more phosphorothioate internucleotide linkages; and wherein said target RNA is encoded by a mammalian gene or is viral RNA. Claim 24 is

dependent on claim 16 and includes all the limitations of claim 16 with the further limitation of a composition comprising the double stranded nucleic acid molecule of claim 16 in a pharmaceutically acceptable carrier or diluent. Applicant is reminded that the instant claims have been afforded priority to the filing date of the instant application, which is November 17, 2003.

Fire et al. teach the advantage of targeting and inhibition of a target gene of known sequence using compositions comprising a pharmaceutically acceptable diluent and further comprising an siRNA molecule between 12-30 nucleobases in length compared to using other inhibitory oligonucleotide molecules such as antisense or ribozymes, which siRNA molecules comprise sequences sharing 100% homology with the complement of the target gene, and full complementarity between strands within the siRNA molecules (see the Abstract, columns 7-11, and claims 1-11).

Zamore et al. teach that 21-23 nucleobases are an optimal size range of siRNAs for the targeting and cleavage of mRNA *in vitro* (see text and Figures on pages 27-32).

Elbashir et al. teach RNA interference (RNAi) is a newly discovered pathway of inhibiting gene expression by using an antisense-like mechanism. Specifically, Elbashir et al. teach short interfering RNAs (siRNAs) as mediators of RNAi and inhibitors of gene expression. Detailed protocols and methods are provided for designing, preparing, testing, and using siRNA to silence/inhibit expression of virtually any known gene. Elbashir et al. teach siRNAs, wherein each strand is 21-23 nucleotides in length and wherein at least 19 nucleotides of the sense strand are complementary to the antisense strand (see Abstract). Elbashir et al. teach modification of the internal nucleotides with

2'-deoxy or 2'-O-methyl modifications (see Abstract and Figure 4). For example, Elbashir et al. teach complete substitution (e.g. 100%) of one or both siRNA strands by 2'-deoxy residues and complete substitution by 2'-O-methyl residues (see page 6882, first column). It is noted that complete substitution of one or both siRNA strands by 2'-deoxy residues or by 2'-O-methyl residues abolished RNAi activity, however, the instant claims do not recite any functional language, therefore, the skilled artisan would have been motivated to incorporate such substitutions/chemical modifications to a siRNA molecule as discussed below.

Neither Fire et al., Zamore et al., nor Elbashir et al. teach siRNA molecules comprising 5' and/or 3' caps, inverted nucleotides or deoxynucleotides and/or inverted abasic moieties, or one or more phosphorothioate internucleotide linkages.

McCall et al. teach chemically synthesized double stranded nucleic acid molecules between about 14 and about 24 nucleotides in length comprising 5' and/or 3' caps comprising inverted (deoxy)abasic moieties, phosphorothioate internucleotide linkages, 2'-O-methyl or 2'-fluoro modified nucleotides, and a target region complementary to a viral or mammalian target gene, which nucleic acid molecule is in a pharmaceutically acceptable diluent (see entire document, especially columns 5, 6, 8-10, and 14).

Matulic-Adamic et al. teach chemically synthesized double stranded nucleic acid molecules between about 14 and about 24 nucleotides in length comprising 5' and/or 3' caps comprising inverted (deoxy)abasic moieties, phosphorothioate internucleotide linkages, 2'-O-methyl or 2'-fluoro modified nucleotides, and a target region

complementary to a viral or mammalian target gene, which nucleic acid molecule is in a pharmaceutically acceptable diluent (see entire document, especially the Abstract, columns 3, 4, and, Figures 8-10, 13, and 18, and claims 1, 4-7, 9, 10, 16-39 and 41).

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to design a chemically modified double stranded short interfering ribonucleic acid (siRNA) molecule comprising a sense strand and an antisense strand, wherein each strand is about 14 to about 24 nucleotides in length, wherein the antisense strand comprises about 14 to about 24 nucleotides that are complementary to a nucleotide sequence of a target RNA or a portion thereof; the sense and the antisense strand are 100% complementary to each other; either the sense or antisense strand comprise a 5'-cap, a 3'-cap or both a 5' and 3'-cap; and about 50 to 100 percent of the nucleotides of the sense strand, the antisense strand, or both comprise a chemical modification wherein the chemical modification is 2'-fluoro, 2'-O-methyl, 2'H, or a combination there using the combined teachings and motivation of Fire et al., Zamore et al., or Elbashir et al., the combination in view of McCall et al. and Matulic-Adamic et al.

It would have been *prima facie* obvious to design and chemically synthesize siRNA molecules with fully complementary strands of about 14 to about 24 nucleotides in length for the targeting and inhibition of expression of mammalian or viral target genes of known sequence because Fire et al. teaches the advantages of using siRNA as inhibitory molecules and Zamore teaches the optimal size range for these inhibitory molecules to be between 21-23 nucleobases. It would have been obvious to have

about 50% to 100% of the nucleotides of the sense and/or the antisense strand of the siRNA comprise a chemical modification, including a 2'-O-methyl modification, since Elbashir et al. taught the desire to apply high percentages of chemical modifications siRNA to determine overall RNAi activity. One of ordinary skill in the art would have expected that siRNA molecules within this size range, comprising perfect complementarity between strands within the siRNA molecule, and chemical modifications to be advantageous in inhibiting the expression of a known target gene *in vitro* because Fire et al. and Elbashir et al. teach the enhanced ability to inhibit expression of a target gene using modified siRNA compared to other inhibitory oligonucleotides, including antisense and ribozymes.

It would have been obvious to one of ordinary skill in the art to incorporate 5' and/or 3'-caps comprising inverted (deoxy)abasic moieties, phosphorothioate internucleotide linkages, 2'-O-methyl or 2'-fluoro nucleotides modifications previously described by many and well known in the art because McCall et al. and Matulic-Adamic both teach the routine use and incorporation of such modifications increase polynucleotide and oligonucleotide stability. The cited art demonstrates that the specific modifications were extensively described in the art. One of skill in the art would be motivated to test modifications that are known to benefit oligonucleotide delivery and stability and apply each of them to a double stranded nucleic acid molecule, including a siRNA, in order to optimize delivery of the nucleic acid. One of skill in the art would be motivated to incorporate chemical modifications to about 50% to 100% of the nucleotide positions in one or both of the strands of the nucleic acid molecule to test the overall

effect on RNAi activity as taught by Elbashir et al.

One of ordinary skill in the art would have been motivated to design siRNA with perfect complementarity between strands and comprising target regions for mammalian or vial target genes because Fire et al., Zamore et al., and Elbashir et al. teach the use of siRNA molecules, including those with perfect complementarity, for target gene inhibition and McCall and Matulic-Adamic also teach the targeting and inhibition of mammalian or viral target genes using inhibitory oligonucleotides. One of ordinary skill in the art would have expected that the design and synthesis of siRNA molecules comprising the well known modifications including 5' and/or 3' caps comprising inverted (deoxy)abasic moieties, phosphorothioate internucleotide linkages, 2'-O-methyl or 2'-fluoro modified nucleotides would provide inhibitory molecules with enhanced stability and a longer biological half-life for a molecule provides for enhanced activity and resulting target gene inhibition.

For these reasons, the instant invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

It is noted that a similar rejection was made of record in the previous Office Action mailed October 29, 2006. In response to this rejection, Applicants argue that the instant rejection has not established a *prima facie* case of obviousness. Applicants argue that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references

themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references when combined must teach or suggest all the claim limitations.

This argument has been fully considered but is not found persuasive because, as discussed above, in totality, the references render the instant application obvious and demonstrate that one of ordinary skill in the art would have been motivated and expected success in making and using the current invention at the time of filing.

Applicants contend that the cited references, alone or in combination fail to teach or suggest all the elements of the claimed invention. Applicants argue that the Office is applying an "obvious to try" rationale in support of its obviousness rejection. Applicants argue that "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful".

Applicant's arguments and contentions have been fully considered, but are not found persuasive because as discussed above, the newly applied reference of Elbashir et al. explicitly teach siRNAs comprising a sense stand and an antisense strand, each strand being about 14 to about 24 nucleotides in length, 100% complementary to a target RNA, and wherein about 50% to 100% of the nucleotides in the sense strand comprise chemical modifications. Elbashir et al. even go so far as to teach specific chemical modification embodiments of the siRNA, including 2'-O-methyl modifications.

While Elbashir et al. do not teach that either the sense or antisense strand comprise cap structure(s), either Matulic-Adamic or McCall teach double stranded nucleic acid inhibitors of gene expression which comprise cap structures. Therefore, the cited art clearly teach the introduction of chemical modifications and those modifications that can be tolerated in double stranded molecules, including siRNA molecules. Thus, contrary to Applicant's contentions, this rejection is not based on an "obvious to try' rationale since the explicit teachings of Elbashir et al., combined with the teachings of either Matulic-Adamic or McCall would arrive at the design instant invention.

Applicants next argue that while the disclosures of Fire and Zamore generally discuss targeting siRNAs of various sizes, the Office acknowledges that these references fail to teach or suggest siRNA molecules comprising the cap structure(s), 2'-modifications, including 2'-fluoro, 2'-O-methyl, and phosphorothioate linkages. Applicants argue that the Office relies on the disclosures of Matulic-Adamic and McCall to cure this deficiency, however these references fail to teach or suggest targeting any RNA sequence using double stranded siRNA, but instead disclose ribozymes. Applicants contend that although ribozymes and siRNA are both nucleic acid-based technologies, they differ substantially both mechanistically and structurally, particularly in relation to the chemical modification strategies that allow such molecules to remain active.

These arguments and contentions have been fully considered, but are not found persuasive because while the references of Matulic-Adamic and McCall teach ribozymes, not siRNAs, as Applicants acknowledge, ribozymes and siRNAs are both

nucleic acid-based technologies. Applicant is reminded that it is obvious to substitute one functional equivalent for another, particularly when they are to be used for the same purpose. See MPEP 2144.06.

Applicants next contend that the modifications taught by Matulic-Adamic and McCall relate primarily to single stranded nucleic acid constructs and do not provide any insight or guidance as to particular chemical modifications that could be incorporated into any double stranded siRNAs, including those of Fire or Zamore, that would still allow for a functional molecule.

This contention has been fully considered, but is not found persuasive because the modifications taught by Matulic-Adamic and McCall provide clear insight as to the chemical modifications that could be incorporated into a double stranded siRNA. For example, and as discussed above, the cited art demonstrates that the specific modifications were extensively described in the art. One of skill in the art would be motivated to test modifications that are known to benefit oligonucleotide delivery and stability and apply each of them to a double stranded nucleic acid molecule, including a siRNA, in order to optimize delivery of the nucleic acid. Further, the newly applied reference of Elbashir et al. teach siRNA comprising complete substitutions of 2'-fluoro or 2'-O-methyl chemical modifications. While Elbashir et al. teach that complete 2'-O-methyl substitution of siRNA completely abolishes RNAi activity, it is noted that the claims do not recite any functional language. Therefore, one of ordinary skill in the art would be motivated to have about 50% to 100% of the nucleotides of the sense or antisense strands of the siRNA comprise chemical modifications, including a 2'-O-

methyl modification as claimed for the purpose of determining overall RNAi activity.

Applicants finally argue that later publications discuss chemically modified siRNA molecules and how the introduction of many chemical modifications can impair or extinguish siRNA activity. Applicants contend that because the Office has failed to cite any art addressing the introduction of chemical modifications that can be tolerated in siRNA molecules, and later publications in the siRNA art expressly teach that extensive modification can obliterate siRNA activity, it could not have been obvious to make the highly modified constructs now being claimed.

Applicants arguments and contentions have been fully considered, but are not found persuasive because, as discussed above, Elbashir et al. explicitly teach siRNAs comprising a sense stand and an antisense strand, each strand being about 14 to about 24 nucleotides in length, 100% complementary to a target RNA, and wherein about 50% to 100% of the nucleotides in the sense strand comprise chemical modifications. Elbashir et al. even go so far as to teach specific chemical modification embodiments of the siRNA, including 2'-O-methyl modifications. While Elbashir et al. do not teach that either the sense or antisense strand comprise cap structure(s), either Matulic-Adamic or McCall teach double stranded nucleic acid inhibitors of gene expression which comprise cap structures. Therefore, the cited art clearly teach the introduction of chemical modifications and those modifications that can be tolerated in double stranded molecules, including siRNA molecules. While Elbashir et al. teach that complete 2'-O-methyl substitution of siRNA completely abolishes RNAi activity, it is noted that the claims do not recite any functional language. Therefore, one of ordinary skill in the art

would be motivated to have about 50% to 100% of the nucleotides of the sense or antisense strands of the siRNA comprise chemical modifications, including a 2'-O-methyl modification as claimed for the purpose of determining overall RNAi activity.

Therefore, in view of the foregoing, claims 16-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al. (U.S. Patent No. 6,506,559), Zamore et al. (Cell, 2000 Vol. 101, pages 25-33), both made of record in the Office Action mailed October 19, 2006), or Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pp. 6877-6888, 2001), the combination in view of McCall et al. (U.S. Patent No. 6,277,634) and Matulic-Adamic et al. (U.S. Patent No. 5,988,203), both made of record in the Office Action mailed April 14, 2006.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published

applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Terra Cotta Gibbs/
June 1, 2007